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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/642,068	STUELPNAGEL ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,7,10,27,33,35-37,54,57,58 and 61-74* is/are pending in the application.

4a) Of the above claim(s) *68-72 and 74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,7,10,27,33,35-37,54,57,58, 61-67 and 73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to amendments filed June 20, 2008 and September 29, 2008. Claims 3-5, 7, 9, 10, 27-30, 33-37 and 52-60 were previously pending. Applicants cancelled claims 5, 9, 28-30, 34, 52, 53, 55, 56, 59 and 60; amended claims 3, 4, 7, 10, 27, 33, 35-37, 54, 57 and 58, and added new claims 61-74. Claims 3, 4, 7, 10, 27, 33, 35-37, 54, 57, 58 and 61-74 are pending.

2. The pending claims were subject to an election of species requirement which was mailed to Applicants on September 4, 2008.

3. Applicant's election with traverse of specie A (claims 58 and 73) in the reply filed on September 29, 2008 is acknowledged. The traversal is on the ground(s) that "amplification" encompasses not only PCR, but rolling circle amplification and LCR. This is not found persuasive because, as stated in the requirement, one reason for the election of species is whether they present different issues with respect to 35 U.S.C. 112, first paragraph. As the enablement issues for the methods performed using PCR differ from the issues involving RCA or LCR, the requirement for the election of species is proper.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 68-72 and 74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 29, 2008.

5. Claims 3, 4, 7, 10, 27, 33, 35-37, 54, 57, 58, 61-67 and 73 will be examined.

6. Applicants' claim cancellations and amendments overcame all of the previously pending rejections.

7. This office action contains new grounds for rejection necessitated by amendment. Applicants' arguments are moot in view of new grounds for rejection.

Claim interpretation

8. The following interpretation of claim limitations is used to evaluate correspondence between the current claims and prior art:

A) Applicants defined the term “pool” in the following way (page 8, last paragraph): “By "pool" is meant a plurality or more than one solution-phase oligonucleotide.”

B) The term “chip” in claim 37 is interpreted as any substrate (it is used interchangeably with “substrate” in the claim). Applicants’ definition on page 16, fourth paragraph: “… By "chip" or biochip" herein is meant a planar substrate to which nucleic acids are directly or indirectly attached.”

C) Applicants did not define the term “array” therefore any arrangement of oligonucleotides bound to a solid support is considered to be an array.

D) Applicants did not define the term “modifying oligonucleotides”, therefore any reaction involving the oligonucleotides is considered to be their modification.

E) The term "different beads" in claim 61 is interpreted as beads which are either structurally different from each other, i.e., have different sizes, or that are different by fact that they are associated with different oligonucleotides, That is, oligonucleotides with different sequences.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 61, 3, 4, 10, 36, 57, 58, 62, 64-67 and 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A) Claims 61, 3, 4, 10, 36, 57, 58, 65-67 and 73 are rejected in claim 61 over the limitation "different beads" in line 1 of step a). There is no support in the specification or in the claims as originally filed for this limitation. Applicants point to claims 28 and 34 and Figure 3 as allegedly providing support for this limitation. However, claims 28 and 34 contained the limitation "first and second beads", but there was no limitation or disclosure anywhere in the specification that the beads need to be different. Therefore, with respect to the beads alone, this limitation is not supported, therefore it constitutes a new matter.

B) Claims 62 and 65 introduce new matter in a limitation "substrate comprises greater than 400 different nucleotides". Applicants stated that support for this limitation is provided in U.S. Patent No. 5,807,522 (at column 14, lines 21-23 and Figure 5), which was incorporated by reference into the instant specification. However, this is what the cited paragraph states:

"In the embodiment shown in FIG. 5, the microarray contains 400 regions in an area of about 16 mm^2, or 2.5 $x10^3$ regions/cm^2."

Therefore, while this paragraph provides support for 400 loci, it does not provide support for more than 400 loci, thus this limitation represents new matter.

C) Claims 64 and 67 introduce new matter in a limitation "substrate comprises greater than 2000 different nucleotides". Applicants stated that support for this limitation is provided in U.S. Patent No. 5,700,637 (at column 7, lines 23-31), which was incorporated by reference into the instant specification. However, this is what the cited paragraph states:

"Where sequence variations are known, an advantage of using this technique is that many different mutations can be probed simultaneously by laying down stripes corresponding to each allelic variant. With a density of one oligonucleotide per mm, and one "individual" per 5 mm, it should be possible to analyse 2000 loci on a plate 100 mm square. Such a high density of information, where the oligonucleotides do identify specific alleles, is not available by other techniques."

Therefore, while this paragraph provides support for 2000 loci, it does not provide support for more than 2000 loci, thus this limitation represents new matter.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 7, 10, 27, 33, 35-37, 57, 58, 61-67 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Science, vol. 280, pp. 1077-1082, May 1998; cited in the previous office action) and Lipshutz et al. (U.S. Patent No. 6,013,440 A; cited in the previous office action), as evidenced by Lashkari et al. (PNAS USA vol. 92, pp. 7912-7915, 1995; cited in the previous office action), Sinha et al. (Nucl. Acids Res., vol. 12, pp. 4539-4557; cited in the previous office action) and Weiler et al. (Anal. Biochem., vol. 243, pp. 218-227, 1996; cited in the previous office action).

Since claims 33 and 35 are restated versions of claim 27, and claim 61 differs from claims 27, 33 and 35 by the support being beads, only steps of claim 27 are discussed explicitly, i.e., claims 27, 33, 35 and 61 are considered together in claim 27.

A) Regarding claims 27, 33, 35 and 61, Wang et al. teach a method of multiplex detection of target nucleic acids, the method comprising:

a) providing a first substrate comprising greater than 50 different oligonucleotides linked to said first substrate through cleavable linkers, said greater than 50 different oligonucleotides having sequences different from each other, wherein said substrate comprises an array of discrete sites to which said greater than 50 different oligonucleotides are covalently linked (Wang et al. teach amplification primer sets for amplifying 46, 92 or 558 loci, therefore they inherently teach

at least 50 different oligonucleotides, since each primer set contains two primers (page 1080, second and third paragraphs). Since oligonucleotides are usually synthesized on an automatic synthesizer, like the one described by Lashkari et al. (Abstract; page 7914 and 7915), it would have been obvious to use such machine by Wang et al., to automate and scale up the synthesis process. Therefore, synthesis of oligonucleotides involved solid support with at least 50 different oligonucleotides synthesized, as evidenced by Lashkari et al.);

b) cleaving said linkers, thereby releasing said greater than 50 different oligonucleotides from said substrate thereby generating a pool of oligonucleotides comprising said greater than 50 different oligonucleotides (Wang et al. inherently teach cleaving the oligonucleotides from the support, since the oligonucleotides are in the purified form and unattached to the substrate, since they were used in the amplification reactions (page 1082, reference 26).);

c) contacting said pool of oligonucleotides with a composition comprising different target nucleic acids, whereby said different target nucleic acids hybridize with said greater than 50 different oligonucleotides (Wang et al. teach multiplex amplification of 46, 92 or 558 different fragments in a single reaction, therefore they inherently teach hybridization of at least 50 primers to their respective six target sequences (page 1080, second and third paragraphs).);

d) modifying said greater than 50 diferent oligonucleotides in said pool of oligonucleotides hybridized with said different target nucleic acids to produce modified oligonucleotides (Wang et al. teach multiplex amplification of 46, 92 or 558 different fragments in a single reaction, therefore they inherently teach hybridization of at least 50 primers to their respective six target sequences and extension (=modification) of the primers to produce amplicons (page 1080, second and third paragraphs; page 1082, reference 26).);

e) contacting said modified oligonucleotides with a second substrate comprising probe oligonucleotides, said probe oligonucleotides having sequences different from each other and having sequences different from said greater than 50 different oligonucleotides released from said first substrate, whereby said target nucleic acids are detected (Wang et al. teach contacting the amplified (=modified) sequences with an array of capture probes which have sequences different from each other and from the primers to detect the amplified sequences (Fig. 1 and 3; page1078, second paragraph; page 1080, first and second paragraphs).).

Regarding claims 57, 58 and 73, Wang et al. teach PCR, therefore they teach amplification (page 1080, second and third paragraphs; page 1082, reference 26).

B) Wang et al. do not teach obtaining the primers from a pool of oligonucleotides released from a support it was synthesized on.

C) Lipshutz et al. teach a method of obtaining oligonucleotide pools.

Regarding claims 27, 33, 35 and 61, Lipshutz et al. teach multiplex detection of target nucleic acids, the method comprising:

a) providing a first substrate comprising greater than 50 different oligonucleotides linked to said first substrate through cleavable linkers, said greater than 50 different oligonucleotides having sequences different from each other, wherein said substrate comprises an array of discrete sites to which said greater than 50 different oligonucleotides are covalently linked (Fig. 1; col. 2, lines 16-37 and 59-62; col. 3, lines 18-35; col. 6, lines 20-48; col. 21, lines 4-33). Lipshutz et al. teach covalent attachment of oligonucleotides to the substrate (col. 17, lines 57-67; col. 18, lines 1-9; col. 21, lines 4-33). Lipshutz et al. teach at least 50 different oligonucleotides (col. 2, lines 16-23; col. 6, lines 32-35).);

b) cleaving said linkers, thereby releasing said greater than 50 different oligonucleotides from said substrate thereby generating a pool of oligonucleotides comprising said greater than 50 different oligonucleotides (col. 2, lines 59-62; col. 21, lines 4-33); and

c) contacting said greater than 50 different oligonucleotides with a composition comprising different target nucleic acids, whereby said target nucleic acids hybridize with said greater than 50 different oligonucleotides whereby said target nucleic acids are detected (col. 2, lines 24-26; col. 3, lines 46-67; col. 4, lines 1-67; col. 5, lines 1-23; col. 7, lines 34-42; col. 8, lines 12-67; col. 9, lines 1-67; col. 10, lines 1-13).

Regarding claim 61, Lipshutz et al. do not specifically teach the substrate being beads. However, they teach synthesis of oligonucleotides on controlled pore glass (CPG) (col. 21, line 7) and synthesis by the method of Sinha et al. (col. 20, lines 24, 25). Sinha et al. teaches synthesis of oligonucleotides on CPG beads (page 4544, last paragraph). Therefore, by teaching synthesis of oligonucleotides by the method of Sinha et al. Lipshutz et al. inherently teach synthesis on glass beads.

Regarding claim 7, Lipshutz et al. teach a substrate with a discrete sites (col. col. 16, lines 47-66).

Regarding claim 10, Lipshutz et al. teach printing and photolithography (col. 16, lines 47-67; col. 17, lines 18-67; col. 18-19).

Regarding claim 36, Lipshutz et al. teach glass (col. 17, lines 57, 58).

Regarding claim 37, Lipshutz et al. teach a chip (col. 17, lines 13-16 and 57-60).

Regarding claims 62-67, Lipshutz et al. teach at least 400, at least 1000 and at least 2000 different oligonucleotides (col. 6, lines 32-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the oligonucleotide pools of Lipshutz et al. as primers in the SNP detection method of Wang et al. with a reasonable expectation of success. One of ordinary skill in the art faced with the teachings of Wang et al. and Lipshutz et al. would have a choice of how the primers used in the multiplex amplification reaction were obtained, i.e., by the method of oligonucleotide pool synthesis of Lipshutz et al.or by an equivalent method using automatic DNA synthesizers, as was customary in the art. However, in view of teaching of Weiler et al. (Anal. Biochem., vol. 243, pp. 218-227, 1996), one of ordinary skill in the art might be motivated to choose the method of Lipshutz et al. Specifically, Weiler et al. teach synthesis of oligonucleotides on polypropylene sheets (= solid support) in such a way that the oligonucleotides could either remain bound to the support or could be cleaved and used as primers in an amplification reaction (Abstract; page 219; page 220, paragraphs 1-4; Fig. 6; Fig. 7; page 224, second, fourth and fifth paragraphs; page 226, first paragraph). Weiler et al. found that the quality of oligonucleotides synthesized on the array was sufficient to produce the same results as commercially available primers, even though they were not further purified after being released from the substrate (Fig. 7 and 8; page 224, second, fourth and fifth paragraphs; page 226, first paragraph). Therefore, one clear advantage of using primers synthesized on an array would be that they needed no further purification steps after being released from the substrate, unlike primers synthesized of commercially available DNA synthesizers, such as the one used by Wang et al. Weiler et al. points to other advantages of using oligonucleotides immobilized on arrays (page 226, last paragraph):

"The complete and efficient separation of nucleobase deprotection and release from the solid support, the stability of the succinate linker during hybridization, and the high quality of the oligomer molecules suggest a combined use of the arrays both as an instrument for screening experiments and as source for oligonucleotide primers. Thereby, an oligomer could first serve as a detector molecule, immediately followed by its use for an isolation of the appropriate DNA fragment by PCR or a direct tag sequence analysis of the region. Also, oligonucleotides identified by hybridization of a given DNA could in turn be used as probes for the identification of homologous fragments, for example, an approach that would simplify and speed up comparative genome analyses. For some applications, it might be necessary to introduce a stretch of unspecific bases at the 3' terminus in order to ensure an enzymatic extension of the molecules by a polymerase. Due to combinatorial constraints, only a moderate number of sequence variations can be synthesized in parallel on a device of a type as depicted in Fig. 1. Nevertheless, such kind of array is of interest for diagnostic applications, for example. Moreover, the results suggest that ultimately even a larger number of independent oligonucleotides could be generated by an appropriately adjusted device. This could make techniques that require small amounts of different oligonucleotides such as primer walking sequencing even more functional."

Therefore, one of ordinary skill in the art at the time of the invention, faced with the choice of which method of synthesis of oligonucleotides to use for production of primers in multiplex amplifications would be motivated to use the method of pool synthesis of Lipshutz et al. in view of clear evidence from Weiler et al. that the primers could be used directly after cleavage from support, therefore saving time and expense required purification of oligonucleotides obtained from standard synthesis. Further, having the oligonucleotides

immobilized on a support provided a clear advantage of being able to use them simultaneously in different assays, such as solution phase PCR and hybridization detection.

Finally, there would be a reasonable expectation of success as evidenced by Wang et al. to successfully amplify sets of 23, 46 or 92 loci, requiring 46, 92 or 184 primers in a single reaction, respectively (page 1080, third paragraph). Further, Wang at al. amplified 558 loci simultaneously with 50% success rate, i.e., a pool of 558 primers worked properly in a single PCR multiplex reaction.

14. Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Science, vol. 280, pp. 1077-1082, May 1998; cited in the previous office action) and Lipshutz et al. (U.S. Patent No. 6,013,440 A; cited in the previous office action), as evidenced by Lashkari et al. (PNAS USA vol. 92, pp. 7912-7915, 1995; cited in the previous office action), Sinha et al. (Nucl. Acids Res., vol. 12, pp. 4539-4557; cited in the previous office action) and Weiler et al. (Anal. Biochem., vol. 243, pp. 218-227, 1996; cited in the previous office action), as applied to claims 27, 34, 35 and 61 above, and further in view of Nelson et al. (Nucl. Acids Res., vol. 20, pp. 6253-6259, 1992; cited in the previous office action).

A) Lipshutz et al. teach fluorescence detection of hybrids (col. 25, lines 43-46), but do not teach labeling of the synthesized oligonucleotides.

B) Regarding claims 3 and 4, Nelson et al. teach labeling oligonucleotides during the synthesis step using labeled phosphoramidites (Abstract; page 6255, last paragraph; page 6256, paragraphs 1-5; Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have labeled the oligonucleotides of Lipshutz et al. and Wang et al.using the

method of Nelson et al. The motivation to do so, provided by Nelson et al., would have been that the oligonucleotides were used directly in PCR amplification and quantitation, mRNA isolation, FISH analysis, antisense gene regulation, DNA fragment analysis and triple helix formation (page 6258, last paragraph).

15. Claim 54 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Science, vol. 280, pp. 1077-1082, May 1998; cited in the previous office action) and Lipshutz et al. (U.S. Patent No. 6,013,440 A; cited in the previous office action), (as evidenced by Lashkari et al. (PNAS USA vol. 92, pp. 7912-7915, 1995; cited in the previous office action), Sinha et al. (Nucl. Acids Res., vol. 12, pp. 4539-4557; cited in the previous office action) and Weiler et al. (Anal. Biochem., vol. 243, pp. 218-227, 1996; cited in the previous office action)), Walt et al. (U.S. Patent No. 6,327,410 B1; cited in the previous office action) and Michael et al. (Anal. Chem., vol. 70, pp. 1242-1248, April 1998; cited in the previous office action).

A) Regarding claim 54, Wang et al. teach a method of multiplex detection of target nucleic acids, the method comprising:

a) providing a first substrate comprising greater than 50 different oligonucleotides linked to said first substrate through cleavable linkers, said greater than 50 different oligonucleotides having sequences different from each other, wherein said substrate comprises an array of discrete sites to which said greater than 50 different oligonucleotides are covalently linked (Wang et al. teach amplification primer sets for amplifying 46, 92 or 558 loci, therefore they inherently teach at least 50 different oligonucleotides, since each primer set contains two primers (page 1080, second and third paragraphs). Since oligonucleotides are usually synthesized on an automatic synthesizer, like the one described by Lashkari et al. (Abstract; page 7914 and 7915), it would

have been obvious to use such machine by Wang et al., to automate and scale up the synthesis process. Therefore, synthesis of oligonucleotides involved solid support with at least 50 different oligonucleotides synthesized, as evidenced by Lashkari et al.);

b) cleaving said linkers, thereby releasing said greater than 50 different oligonucleotides from said substrate thereby generating a pool of oligonucleotides comprising said greater than 50 different oligonucleotides (Wang et al. inherently teach cleaving the oligonucleotides from the support, since the oligonucleotides are in the purified form and unattached to the substrate, since they were used in the amplification reactions (page 1082, reference 26).);

c) contacting said pool of oligonucleotides with a composition comprising different target nucleic acids, whereby said different target nucleic acids hybridize with said greater than 50 different oligonucleotides (Wang et al. teach multiplex amplification of 46, 92 or 558 different fragments in a single reaction, therefore they inherently teach hybridization of at least 50 primers to their respective six target sequences (page 1080, second and third paragraphs).);

d) modifying said greater than 50 diferent oligonucleotides in said pool of oligonucleotides hybridized with said different target nucleic acids to produce modified oligonucleotides (Wang et al. teach multiplex amplification of 46, 92 or 558 different fragments in a single reaction, therefore they inherently teach hybridization of at least 50 primers to their respective six target sequences and extension (=modification) of the primers to produce amplicons (page 1080, second and third paragraphs; page 1082, reference 26).);

e) contacting said modified oligonucleotides with a second substrate comprising probe oligonucleotides, said probe oligonucleotides having sequences different from each other and having sequences different from said greater than 50 different oligonucleotides released from

said first substrate, whereby said target nucleic acids are detected (Wang et al. teach contacting the amplified (=modified) sequences with an array of capture probes which have sequences different from each other and from the primers to detect the amplified sequences (Fig. 1 and 3; page1078, second paragraph; page 1080, first and second paragraphs).).

B) Wang et al. do not teach obtaining the primers from a pool of oligonucleotides released from a support it was synthesized on.

C) Lipshutz et al. teach a method of obtaining oligonucleotide pools.

Regarding claim 54, Lipshutz et al. teach multiplex detection of target nucleic acids, the method comprising:

a) providing a first substrate comprising greater than 50 different oligonucleotides linked to said first substrate through cleavable linkers, said greater than 50 different oligonucleotides having sequences different from each other, wherein said substrate comprises an array of discrete sites to which said greater than 50 different oligonucleotides are covalently linked (Fig. 1; col. 2, lines 16-37 and 59-62; col. 3, lines 18-35; col. 6, lines 20-48; col. 21, lines 4-33). Lipshutz et al. teach covalent attachment of oligonucleotides to the substrate (col. 17, lines 57-67; col. 18, lines 1-9; col. 21, lines 4-33). Lipshutz et al. teach at least 50 different oligonucleotides (col. 2, lines 16-23; col. 6, lines 32-35).);

b) cleaving said linkers, thereby releasing said greater than 50 different oligonucleotides from said substrate thereby generating a pool of oligonucleotides comprising said greater than 50 different oligonucleotides (col. 2, lines 59-62; col. 21, lines 4-33); and

c) contacting said greater than 50 different oligonucleotides with a composition comprising different target nucleic acids, whereby said target nucleic acids hybridize with said

greater than 50 different oligonucleotides whereby said target nucleic acids are detected (col. 2, lines 24-26; col. 3, lines 46-67; col. 4, lines 1-67; col. 5, lines 1-23; col. 7, lines 34-42; col. 8, lines 12-67; col. 9, lines 1-67; col. 10, lines 1-13).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the oligonucleotide pools of Lipshutz et al. as primers in the SNP detection method of Wang et al. with a reasonable expectation of success. One of ordinary skill in the art faced with the teachings of Wang et al. and Lipshutz et al. would have a choice of how the primers used in the multiplex amplification reaction were obtained, i.e., by the method of oligonucleotide pool synthesis of Lipshutz et al.or by an equivalent method using automatic DNA synthesizers, as was customary in the art. However, in view of teaching of Weiler et al. (Anal. Biochem., vol. 243, pp. 218-227, 1996), one of ordinary skill in the art might be motivated to choose the method of Lipshutz et al. Specifically, Weiler et al. teach synthesis of oligonucleotides on polypropylene sheets (= solid support) in such a way that the oligonucleotides could either remain bound to the support or could be cleaved and used as primers in an amplification reaction (Abstract; page 219; page 220, paragraphs 1-4; Fig. 6; Fig. 7; page 224, second, fourth and fifth paragraphs; page 226, first paragraph). Weiler et al. found that the quality of oligonucleotides synthesized on the array was sufficient to produce the same results as commercially available primers, even though they were not further purified after being released from the substrate (Fig. 7 and 8; page 224, second, fourth and fifth paragraphs; page 226, first paragraph). Therefore, one clear advantage of using primers synthesized on an array would be that they needed no further purification steps after being released from the substrate, unlike primers synthesized of commercially available DNA synthesizers, such as the one used by

Wang et al. Weiler et al. points to other advantages of using oligonucleotides immobilized on arrays (page 226, last paragraph):

"The complete and efficient separation of nucleobase deprotection and release from the solid support, the stability of the succinate linker during hybridization, and the high quality of the oligomer molecules suggest a combined use of the arrays both as an instrument for screening experiments and as source for oligonucleotide primers. Thereby, an oligomer could first serve as a detector molecule, immediately followed by its use for an isolation of the appropriate DNA fragment by PCR or a direct tag sequence analysis of the region. Also, oligonucleotides identified by hybridization of a given DNA could in turn be used as probes for the identification of homologous fragments, for example, an approach that would simplify and speed up comparative genome analyses. For some applications, it might be necessary to introduce a stretch of unspecific bases at the 3' terminus in order to ensure an enzymatic extension of the molecules by a polymerase. Due to combinatorial constraints, only a moderate number of sequence variations can be synthesized in parallel on a device of a type as depicted in Fig. 1. Nevertheless, such kind of array is of interest for diagnostic applications, for example. Moreover, the results suggest that ultimately even a larger number of independent oligonucleotides could be generated by an appropriately adjusted device. This could make techniques that require small amounts of different oligonucleotides such as primer walking sequencing even more functional."

Therefore, one of ordinary skill in the art at the time of the invention, faced with the choice of which method of synthesis of oligonucleotides to use for production of primers in multiplex amplifications would be motivated to use the method of pool synthesis of Lipshutz et al. in view of clear evidence from Weiler et al. that the primers could be used directly after

cleavage from support, therefore saving time and expense required purification of oligonucleotides obtained from standard synthesis. Further, having the oligonucleotides immobilized on a support provided a clear advantage of being able to use them simultaneously in different assays, such as solution phase PCR and hybridization detection.

Finally, there would be a reasonable expectation of success as evidenced by Wang et al. to successfully amplify sets of 23, 46 or 92 loci, requiring 46, 92 or 184 primers in a single reaction, respectively (page 1080, third paragraph). Further, Wang at al. amplified 558 loci simultaneously with 50% success rate, i.e., a pool of 558 primers worked properly in a single PCR multiplex reaction.

D) None of the above references teach detection of nucleic acids on arrays with probes randomly distributed on a substrate.

E) Regarding claim 54, Walt et al. teach microsphere-based analytical chemistry system in which the microspheres are distributed on a fiber optic bundle (Abstract). The surface of the substrate comprises discrete sites into which at least two subpopulations of microspheres are distributed. Each of the microspheres comprises a bioactive agent and an optical signature which allows identification of the bioactive agent. The beads are randomly distributed on the array (col. 3, lines 35-45; col. 4, lines 54-56). The bioactive agent attached to the microsphere is a nucleic acid, particularly a nucleic acid probe (col. 7, lines 55-66; col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). Walt et al. teach the microspheres containing a probe (=identifier binding ligand) which binds a decoder binding ligand (= target nucleic acid) (col. 10, lines 43-47; col. 21, lines 17-60). Since each of the beads contains a unique optical signature (col. 13, lines 8-24), the identity and location of each bead can be determined.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the randomly distributed oligonucleotides bound to microspheres of Walt et al. randomly distributed over the surface of the fiber optic sensor in the method of nucleic acid detection of Wang et al. and Lipshutz et al. The motivation to do so, provided by Walt et al., would have been that (col. 3, lines 13-26):

"The innovation of the two previous patents was the placement of multiple chemical functionalities at the end of a single optical fiber bundle sensor. This configuration yielded an analytic chemistry sensor that could be remotely monitored via the typically small bundle. The drawback, however, was the difficulty in applying the various chemistries associated with the chemical functionalities at the sensor's end; the functionalities were built on the sensor's end in a serial fashion. This was a slow process, and in practice, only tens of functionalities could be applied. Accordingly, compositions and methods are desirable that allow the generation of large fiber optic arrays including microspheres that can be either encoded or decoded to allow the detection of target analytes." and (col. 4, lines 35-56):

"The present invention is based on two synergistic inventions: 1) the development of a bead-based analytic chemistry system in which beads, also termed microspheres, carrying different chemical functionalities may be mixed together while the ability is retained to identify the functionality of each bead using an optically interrogatable encoding scheme (an "optical signature"); and 2) the use of a substrate comprising a patterned surface containing individual sites that can bind or associate individual beads. This allows the synthesis of the bioactive agents (i.e. compounds such as nucleic acids and antibodies) to be separated from their placement on an array, i.e. the bioactive agents may be synthesized on the beads, and then the

beads are randomly distributed on a patterned surface. Since the beads are first coded with an optical signature, this means that the array can later be "decoded", i.e. after the array is made, a correlation of the location of an individual site on the array with the bead or bioactive agent at that particular site can be made. This means that the beads may be randomly distributed on the array, a fast and inexpensive process as compared to either the in situ synthesis or spotting techniques of the prior art."

Further motivation to use such arrays is provided by Michael et al. (Anal. Chem., vol. 70, pp. 1242-1248, April 1998) on page 1247, last paragraph, continued on page 1248:

"We have demonstrated the ability to fabricate randomly ordered, addressable, high-density optical sensor arrays. This approach to preparing array sensors offers a dramatic shift from conventional sensor fabrication procedures which require multiple steps such as photolithography, micromachining, and site-selective syntheses. Microwell arrays are easily and reproducibly fabricated using commercially available imaging fibers without requiring a high degree of precision. One series of chemical reactions can create a stock supply of billions (5.8×10^9 microspheres/mL) of chemically modified sensors with virtually identical properties that can be used in the fabrication of new arrays for different analyte sets. Also, the need to identify every location and to calibrate each sensor in the array is eliminated because only those microspheres giving rise to an analytical signal need to be decoded. This advantage may be of particular value when rapid diagnostic tools are required or when analyses with low "hits" are performed, such as immunodiagnostics or low-frequency mutation analysis with gene arrays. Multiple copies of each sensor are easily represented in each array, providing a level of redundancy that should avoid both false positives and false negatives. The image processing software used to analyze the

spectral information makes this approach advantageous in applications requiring high sample throughput. Since the fabrication process is fast and simple and the materials are inexpensive, there is no economical demand to reuse the array. We are presently extending this work to demonstrate arrays for immunoassays, gene probe sequences, and vapor sensors. Finally, the sensors offer the ultimate flexibility-as new assays come along, new microspheres simply can be added to the existing microsphere mixture at virtually no setup or time cost."

16. No claims are allowed.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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